PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel Aviv
ISRAËL

Date of mailing (day/month/year)
10 November 2000 (10.11.00)

Applicant's or agent's file reference
123335.2 MM

IMPORTANT NOTIFICATION

International application No.
PCT/IL00/00185

International filing date (day/month/year)
24 March 2000 (24.03.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
SHINITZKY, Meir
20 Derech Haganim Street
46910 Rehovot
Israel

State of Nationality: IL
State of Residence: IL
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
SHINITZKY, Meir
20 Derech Haganim Street
46910 Kfar Shmaryahu
Israel

State of Nationality: IL
State of Residence: IL
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
A. Karkachi

Telephone No.: (41-22) 338.83.38

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Interr. ial Application No
PCT/IL 00/00185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/665 A61P43/00 A61P35/00 A61P35/02 A61P3/10
C07F9/6574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	KINOR N ET AL: "Cyclic glycerophosphates for the treatment of Parkinson's disease" NEUROSCI. LETT., vol. 54, no. supp, November 1999 (1999-11), page S24 XP002155523 abstract --- WO 00 09139 A (ALLELIX BIOPHARMA ;BEGLEITER LEATH E (CA); WICKENS PHILIP L (CA);) 24 February 2000 (2000-02-24) abstract page 11, line 11 -page 12, line 10 page 13, line 26 -page 14, line 22; claims; example 1 --- -/--	1-35 1-35

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2000	28/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Orviz Diaz, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 57864 A (SHINITZKY MEIR ;YEDA RES & DEV (IL)) 5 October 2000 (2000-10-05) the whole document	1-35
X	FRIEDMAN P ET AL: "CONVERSION OF LYSOPHOSPHOLIPIDS TO CYCLIC LYSOPHOSPHATIDIC ACID BY PHOSPHOLIPASE D" JOURNAL OF BIOLOGICAL CHEMISTRY,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD,US, vol. 271, no. 2, 12 January 1996 (1996-01-12), pages 953-957, XP000946154 ISSN: 0021-9258 the whole document	1-13
T	SHINITZKY M ET AL: "INDUCTION OF INTRACELLULAR SIGNALING BY CYCLIC GLYCEROPHOSPHATES AND THEIR DEOXY ANALOGUES" EUROPEAN JOURNAL OF BIOCHEMISTRY,BERLIN,DE, vol. 267, no. 9, May 2000 (2000-05), pages 2547-2554, XP000965121 ISSN: 0014-2956 the whole document	1-35
P,X	MUKAI, MUTSUKO ET AL: "Inhibition of tumor invasion and metastasis by a novel lysophosphatidic acid (cyclic LPA)" INT. J. CANCER (1999), 81(6), 918-922, XP000949280 the whole document	1-13
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Tumor metastasis inhibitors containing 1-O-acylglycerol-2,3-phosphates" retrieved from STN Database accession no. 126:220705 XP002148570 abstract & JP 09 025235 A (SAGAMI CHEM RES, JAPAN) 28 January 1997 (1997-01-28)	1-13

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Preparation of 1-O-acylglycerol-2,3-phosphates and DNA polymerase.alpha. inhibitors containing them" retrieved from STN Database accession no. 124:76506 XP002148571 abstract & JP 07 258278 A (SAGAMI CHEM RES, JAPAN) 9 October 1995 (1995-10-09) ---	1-13
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Method for preparation of 1-O-acylglycerol 2,3-cyclic phosphate" retrieved from STN Database accession no. 123:144502 XP002148572 abstract & JP 06 228169 A (SAGAMI CHEM RES, JAPAN) 16 August 1994 (1994-08-16) ---	1-13
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Promoters of protein phosphokinase C activation containing 1-O-acylglycerol 2,3-cyclic phosphate" retrieved from STN Database accession no. 123:350234 XP002148573 abstract & JP 07 149772 A (SAGAMI CHEM RES, JAPAN) 13 June 1995 (1995-06-13) ---	1-13
X	US 5 565 439 A (PIAZZA GARY A ET AL) 15 October 1996 (1996-10-15) abstract column 1, line 60 -column 2, line 39; claims; example II ---	1-13
X	D.C. AYRES ET AL.: "The Organic Chemistry of Phosphorus. Part V." J. CHEM. SOC., 1957, pages 1109-1114, XP000946300 see compounds (VI) and (VII) pages 1111 and 1114 ---	1-13

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REVEL, MONIQUE ET AL: "Phosphorus heterocycles. XXVII. NMR study of 4-monosubstituted 1,3,2-dioxa- and -dithiaphospholane derivatives" ORG. MAGN. RESON. (1976), 8(8), 399-406, XP000949315 page 399 ---	1-13
X	SHINITZKY M ET AL: "Formation of 1,3-cyclic glycerophosphate by the action of phospholipase C on phosphatidylglycerol." JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 JUL 5) 268 (19) 14109-15., XP000946147 figures 6,10 ---	1-13
X	T. UKITA ET AL.: "Organic Phosphates. I. Synthesis of 1,2-Diol Cyclic Phosphates." PHARM. BULL., vol. 5, 1957, pages 121-126, XP000949388 see compounds (I) and (V) pages 122-124 ---	1-13
X	SU, BANGYING ET AL: "Identification of a putative tumor marker in breast and colon cancer" CANCER RES. (1993), 53(8), 1751-4, XP000946184 figure 4 ---	1-13
X	ABBOTT, STEVEN J. ET AL: "Chiral '160, 170, 180!phosphate monoesters. 1. Asymmetric synthesis and stereochemical analysis of '1(R)-160, 170, 180!phospho-(S)-propane-1,2-diol" J. AM. CHEM. SOC. (1978), 100(8), 2558-60, XP000946182 see scheme II page 2558 -----	1-13

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter...nal Application No
PCT/IL 00/00185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0009139 A	24-02-2000	US 6150345 A AU 5473599 A	21-11-2000 06-03-2000
WO 0057864 A	05-10-2000	NONE	
JP 9025235 A	28-01-1997	NONE	
JP 7258278 A	09-10-1995	NONE	
JP 6228169 A	16-08-1994	NONE	
JP 7149772 A	13-06-1995	NONE	
US 5565439 A	15-10-1996	NONE	

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00 | A2

(11) International Publication Number: WO 00/57865

(43) International Publication Date: 5 October 2000 (05.10.00)

(21) International Application Number: PCT/IL00/00185

(22) International Filing Date: 24 March 2000 (24.03.00)

(30) Priority Data:
129178 25 March 1999 (25.03.99) IL

(71) Applicant *(for all designated States except US)*: YEDA RESEARCH AND DEVELOPMENT CO. LTD. [IL/IL]; at the Weizmann Institute of Science, P.O. Box 95, 76100 Rehovot (IL).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: SHINITZKY, Meir [IL/IL]; 20 Derech Haganim Street, 46910 Rehovot (IL).

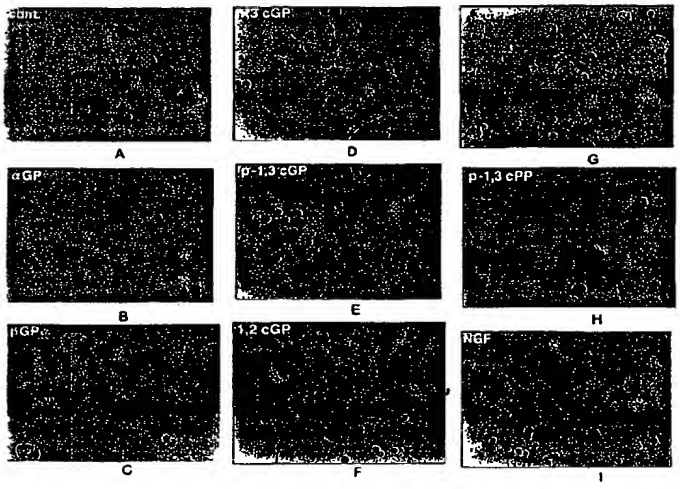
(74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLIC GLYCEROPHOSPHATES AND ANALOGS THEREOF FOR PROMOTING NEURAL CELL DIFFERENTIATION



(57) Abstract

Cyclic glycerophosphates and analogs thereof (CGs) are shown to exert neural promoting activities in target cells. Such activities include promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting envrionment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue. These activities of the CGs render them useful for treatment of various disorders including but not limited to mental disorders such as, for example, schizophrenia, dementia or disorders resulting in learning disablities. In addition, these CGs may be used for the treatment of neurodegenerative conditions such as Altzheimer's diesease, Parkinson's disease, conditions resulting from exposure to harmful environmental factors or resulting from a mechanical injury. The CGs may also be used to treat an individual suffering from a primary neurodengenerative condition in order to prevent or reduce the appearance of secondary degeneration in additional nerves (*"nerve rescue"*).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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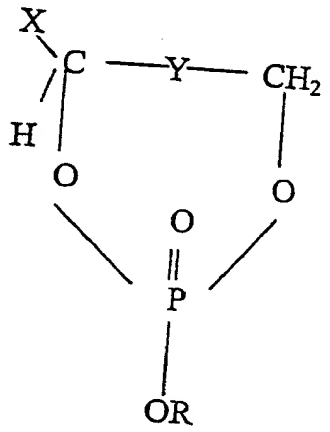
CLAIMS:

1. A pharmaceutical composition for promoting neural cell differentiation in target cells comprising a pharmaceutically acceptable carrier and, as an active ingredient, a compound of the general formula I



wherein

Y is $-(CH_2)_m-$, -CH(OH)- or -C(=O)- , and m is 0 - 3 ;

X is H, alkyl, $-CH_2OH-$, CH_2Oacyl or $-CH_2$acyl; and

R is H, a cation, alkyl or optionally substituted aryl.

2. A pharmaceutical composition for promoting neural activity comprising a pharmaceutical acceptable carrier and, as an active ingredient, a compound of the general Formula I of Claim 1.

3. A pharmaceutical composition according to Claim 2, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.

4. A pharmaceutical composition comprising a pharmaceutical acceptable carrier and, as an active ingredient, a compound of the general Formula I of Claim 1, for the prevention or treatment of disorders and diseases which can be prevented or treated by promoting neural cell differentiation and/or neural activity.

5. A pharmaceutical composition according to Claim 4, wherein said disorders and diseases are mental disorders.

6. A pharmaceutical composition according to Claim 5, wherein said mental disorder is schizophrenia or dementia.

7. A pharmaceutical composition according to Claim 5, wherein said mental disorder is a learning disability.

8. A pharmaceutical composition according to Claim 4, for the treatment of neurodegenerative conditions involving damage to the dopaminergic neural cells.

9. A pharmaceutical composition according to Claim 8, wherein said neurodegenerative condition is Alzheimer's disease.

10. A pharmaceutical composition according to Claim 8, wherein said neurodegenerative condition is Parkinson's disease.

11. A pharmaceutical composition according to Claim 4, wherein said disorders and diseases result from exposure to harmful environmental factors or from a mechanical injury.

12. A pharmaceutical composition according to Claim 4, for the treatment of nerve rescue after nerve injury.

13. A pharmaceutical composition according to any one of Claims 1-12, wherein the active ingredient is a compound of Formula I selected from the group consisting of:

i. 1,3 cyclic glycerophosphate - **1,3 cGP;**

ii. 1,2 cyclic glycerophosphate - **1,2 cGP;**

iii. 3-acyl 1,2 cyclic glycerophosphate (cyclic lysophosphatidic acid) - **c-lysoPA;**

iv. Phenyl 1,3 cGP – **P-1,3 cGP;**

v. Phenyl 1,2 cGP – **P-1,2 cGP;**

vi. 1,3 cyclic propanediol phosphate – **1,3 cPP;**

vii. 1,2 cyclic propanediol phosphate – **1,2 cPP;**

viii. Phenyl 1,3 cPP – **P-1,3 cPP;**

ix. Phenyl 1,2, cyclic propanediol phosphate – **P-1,2, cPP;**

x. Cyclic dihydroxyacetone phosphate – **cDHAP**; and

xi. Phenyl cyclic dihydroxyacetone phosphate - **P-cDHAP.**

14. A method for inducing promotion of neural cell differentiation of target cells comprising contacting said target cells for a suitable period of time with an effective amount of a compound of the general Formula I of Claim 1.

15. A method for promoting neural activity in an individual comprising administering to the individual in need an effective amount of a compound of the general Formula I of Claim 1.

16. A method according to Claim 15, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.

17. A method for the prevention or treatment of disorders and diseases which can be prevented or treated by promoting neural cell differentiation and/or neural activity comprising administering to a person in need a therapeutically effective amount of a compound of Formula I of Claim 1.

18. A method according to Claim 17, wherein said disorders and diseases are mental disorders or diseases.

19. A method according to Claim 18, wherein said mental disorder or disease is schizophrenia or dementia.

20. A method according to Claim 18, wherein said mental disorder is a learning disability.

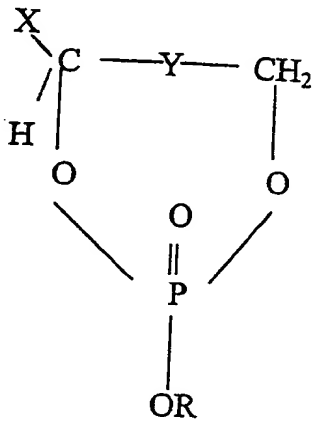
21. A method according to Claim 17, wherein said disorders and diseases are neurodegenerative disorders or diseases.

22. A method according to Claim 21, wherein said neurodegenerative disorder or disease is Alzheimer's disease or Parkinson's disease.

23. A method according to Claim 17, wherein said disorders or diseases result from exposure of an individual to harmful environmental factors or from a mechanical injury.

24. A method according to Claim 15, for the treatment of nerve rescue after nerve injury.

25. Use of a compound of the general Formula I



wherein

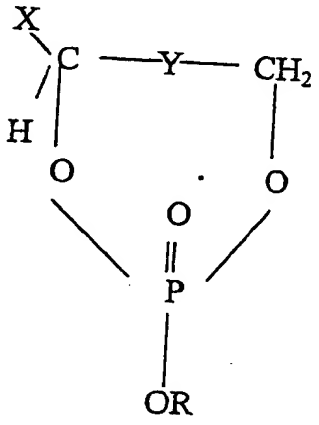
Y is $-(CH_2)_m-$, -CH(OH)- or -C(=O)- , and m is 0 - 3 ;

X is H, alkyl, $-CH_2OH-$, CH_2Oacyl or $-CH_2acyl$; and

R is H, a cation, alkyl or optionally substituted aryl

for the preparation of a pharmaceutical composition for promoting neural cell differentiation.

26. Use of a compound of the general Formula I



wherein

Y is $-(CH_2)_m-$, -CH(OH)- or -C(=O)- , and m is 0 - 3 ;

X is H, alkyl, $-CH_2OH-$, CH_2Oacyl or $-CH_2acyl$; and

R is H, a cation, alkyl or optionally substituted aryl for the preparation of a pharmaceutical composition for promoting neural activity.

27. Use according to Claim 26, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promoting of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.

28. Use according to Claim 25, for the prevention or treatment of disorders and diseases which can be prevented or treated by promoting neural cell differentiation and/or neural activity.

29. Use according to Claim 28, wherein said disorders and diseases are mental disorders or diseases.

30. Use according to Claim 29, wherein said mental disorder or disease is schizophrenia or dementia.

31. Use according to Claim 29, wherein said mental disorder is a learning disability.

32. Use according to Claim 28, wherein said disorders and diseases are neurodegenerative disorders or diseases.

33. Use according to Claim 32, wherein said neurodegenerative disorders or diseases are Alzheimer's disease or parkinson's disease.

34. Use according to Claim 28, wherein said disorders or diseases result from exposure of an individual to harmful environmental factors or from a mechanical injury.

35. Use according to Claim 27, for nerve rescue after nerve injury.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
123335.2 MM		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 00/00185	24/03/2000	25/03/1999
Applicant		
YEDA RESEARCH ADN DEVELOPMENT CO. LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/IL 00/00185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/665 A61P43/00 A61P35/00 A61P35/02 A61P3/10
C07F9/6574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	KINOR N ET AL: "Cyclic glycerophosphates for the treatment of Parkinson's disease" NEUROSCI. LETT., vol. 54, no. supp, November 1999 (1999-11), page S24 XP002155523 abstract ---	1-35
P,X	WO 00 09139 A (ALLELIX BIOPHARMA ;BEGLEITER LEATH E (CA); WICKENS PHILIP L (CA);) 24 February 2000 (2000-02-24) abstract page 11, line 11 -page 12, line 10 page 13, line 26 -page 14, line 22; claims; example 1 --- -/--	1-35

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2000	28/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Orviz Diaz, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 57864 A (SHINITZKY MEIR ;YEDA RES & DEV (IL)) 5 October 2000 (2000-10-05) the whole document	1-35
X	FRIEDMAN P ET AL: "CONVERSION OF LYSOPHOSPHOLIPIDS TO CYCLIC LYSOPHOSPHATIDIC ACID BY PHOSPHOLIPASE D" JOURNAL OF BIOLOGICAL CHEMISTRY,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD,US, vol. 271, no. 2, 12 January 1996 (1996-01-12), pages 953-957, XP000946154 ISSN: 0021-9258 the whole document	1-13
T	SHINITZKY M ET AL: "INDUCTION OF INTRACELLULAR SIGNALING BY CYCLIC GLYCEROPHOSPHATES AND THEIR DEOXY ANALOGUES" EUROPEAN JOURNAL OF BIOCHEMISTRY,BERLIN,DE, vol. 267, no. 9, May 2000 (2000-05), pages 2547-2554, XP000965121 ISSN: 0014-2956 the whole document	1-35
P,X	MUKAI, MUTSUKO ET AL: "Inhibition of tumor invasion and metastasis by a novel lysophosphatidic acid (cyclic LPA)" INT. J. CANCER (1999), 81(6), 918-922, XP000949280 the whole document	1-13
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Tumor metastasis inhibitors containing 1-O-acylglycerol-2,3-phosphates" retrieved from STN Database accession no. 126:220705 XP002148570 abstract & JP 09 025235 A (SAGAMI CHEM RES, JAPAN) 28 January 1997 (1997-01-28)	1-13

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Preparation of 1-O-acylglycerol-2,3-phosphates and DNA polymerase.alpha. inhibitors containing them" retrieved from STN Database accession no. 124:76506 XP002148571 abstract & JP 07 258278 A (SAGAMI CHEM RES, JAPAN) 9 October 1995 (1995-10-09) ---	1-13
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Method for preparation of 1-O-acylglycerol 2,3-cyclic phosphate" retrieved from STN Database accession no. 123:144502 XP002148572 abstract & JP 06 228169 A (SAGAMI CHEM RES, JAPAN) 16 August 1994 (1994-08-16) ---	1-13
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: "Promoters of protein phosphokinase C activation containing 1-O-acylglycerol 2,3-cyclic phosphate" retrieved from STN Database accession no. 123:350234 XP002148573 abstract & JP 07 149772 A (SAGAMI CHEM RES, JAPAN) 13 June 1995 (1995-06-13) ---	1-13
X	US 5 565 439 A (PIAZZA GARY A ET AL) 15 October 1996 (1996-10-15) abstract column 1, line 60 -column 2, line 39; claims; example II ---	1-13
X	D.C. AYRES ET AL.: "The Organic Chemistry of Phosphorus. Part V." J. CHEM. SOC., 1957, pages 1109-1114, XP000946300 see compounds (VI) and (VII) pages 1111 and 1114 --- -/--	1-13

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	REVEL, MONIQUE ET AL: "Phosphorus heterocycles. XXVII. NMR study of 4-monosubstituted 1,3,2-dioxa- and -dithiaphospholane derivatives" ORG. MAGN. RESON. (1976), 8(8), 399-406, XP000949315 page 399 ---	1-13
X	SHINITZKY M ET AL: "Formation of 1,3-cyclic glycerophosphate by the action of phospholipase C on phosphatidylglycerol." JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 JUL 5) 268 (19) 14109-15., XP000946147 figures 6,10 ---	1-13
X	T. UKITA ET AL.: "Organic Phosphates. I. Synthesis of 1,2-Diol Cyclic Phosphates." PHARM. BULL., vol. 5, 1957, pages 121-126, XP000949388 see compounds (I) and (V) pages 122-124 ---	1-13
X	SU, BANGYING ET AL: "Identification of a putative tumor marker in breast and colon cancer" CANCER RES. (1993), 53(8), 1751-4, XP000946184 figure 4 ---	1-13
X	ABBOTT, STEVEN J. ET AL: "Chiral '160, 170, 180!phosphate monoesters. 1. Asymmetric synthesis and stereochemical analysis of '1(R)-160, 170, 180!phospho-(S)-propane-1,2-diol" J. AM. CHEM. SOC. (1978), 100(8), 2558-60, XP000946182 see scheme II page 2558 -----	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
IL 00/00185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0009139 A	24-02-2000	US 6150345 A AU 5473599 A	21-11-2000 06-03-2000
WO 0057864 A	05-10-2000	NONE	
JP 9025235 A	28-01-1997	NONE	
JP 7258278 A	09-10-1995	NONE	
JP 6228169 A	16-08-1994	NONE	
JP 7149772 A	13-06-1995	NONE	
US 5565439 A	15-10-1996	NONE	

1600

PATENT COOPERATION TREATY

PCT

D9/936,922 1617

14

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
123335.2 MM		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL00/00185	24/03/2000	25/03/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant YEDA RESEARCH ADN DEVELOPMENT CO. LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
VI	☒	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/10/2000	29.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giacobbe, S Telephone No. +49 89 2399 8463

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL00/00185

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, pages:

1-28 as originally filed

Claims, No.:

1-36 as received on 19/04/2001 with letter of 17/04/2001

Drawings, sheets:

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-8, 17-26.

because:

   ☒ the said international application, or the said claims Nos. 1-8, 17-26 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-36

	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-36
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	9-16, 27-36
	No:	Claims	1-8, 17-26 (cf. Separate Sheet)

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Section I

The amended claims fulfill the requirements of Art 34(2)(b) PCT in that they do not introduce subject-matter which was not present in the application as originally filed.

2. Section III

Claims 1-8 and 17-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). However, although not required under the provisions of the PCT, an opinion will be given with respect to novelty and inventive step.

3. Section V

3.1 Cited Documents

The following documents (D) are referred to in this Report:

D1: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: 'Promoters of protein phosphokinase C activation containing 1-O-acylglycerol 2,3-cyclic phosphate' retrieved from STN Database accession no. 123:350234 & JP 07 149772 A (SAGAMI CHEM RES, JAPAN) 13 June 1995

D2: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: 'Tumor metastasis inhibitors containing 1-O-acylglycerol-2,3-phosphates' retrieved from STN Database accession no. 126:220705 & JP 09 025235 A (SAGAMI CHEM RES, JAPAN) 28 January 1997

D3: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOBAYASHI, SUSUMU ET AL: 'Preparation of 1-O-acylglycerol-2,3-phosphates and DNA polymerase.alpha. inhibitors containing them' retrieved from STN Database accession no. 124:76506 & JP 07 258278 A (SAGAMI CHEM RES, JAPAN) 9 October 1995

D4: US-A-5 565 439 (PIAZZA GARY A ET AL) 15 October 1996

Document D1 (cf. the whole document) discloses the use of the compounds of formula I for the treatment of dementia, a mental, neurodegenerative

disorder.These molecules have been disclaimed in present independent claims 1 and 10, whereas dementia has been disclaimed in present independent claims 17 and 27.

Document D2 (cf. the whole document) discloses the use of the compounds of formula I for the inhibition of metastasis.

Document D3 (cf. the whole document) discloses the use of the compounds of formula I as antitumour agents.

Document D4 (cf. Abstract and Example II) discloses the use of compounds falling within the scope of the present general formula for treating hyperproliferative conditions.

3.2 Art 33(2) PCT (Novelty)

The subject-matter of present claims 1-36 meets the requirements of Art 33(2) PCT.

Due to the above-mentioned disclaimers none of the available prior art documents anticipates the presently claimed subject-matter.

3.3 Art 33(3) PCT (Inventive step)

The subject-matter of present claims 1-36 meets the requirements of Art 33(3) PCT.

The subject-matter of claims 17-36 (i.e. the use of all the molecules of the general formula for the treatment of all diseases with the exception of dementia), as well as that of claims 1-16 (i.e. the use of the molecules of the general formula remaining after those of D1 are subtracted) for the treatment of mental and neurodegenerative disorders including dementia, are considered as inventive because they solve the technical problem of treating the mentioned diseases in a way which could not be deduced from D1 itself (cf. in this context Examples 12 to 14 and Figure II). It is in particular considered that D1 does not provide any indication that a) compounds other than those described are active in the treatment of dementia or b) neural diseases other than dementia are curable by use of the described compounds.

3.4 Art 33(4) PCT (Industrial applicability)

As stated above, no opinion is given on the question of whether present claims 1-8 and 17-26 are industrially applicable since their patentability is inter alia dependent upon their formulation as well as upon national and regional laws and no unifying criteria is

provided in this field by the PCT.

4. Section VI

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 00/09139	24.2.00	10.8.99	10.8.99
WO 00/57864	5.10.00	24.3.00	25.3.99

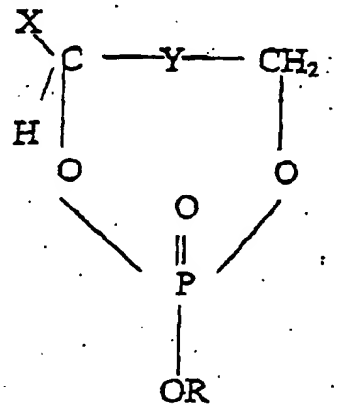
5. Section VIII

Claims 1, 2, 4, 9, 10, 12, 17, 18, 27 and 28 are not clear because the expressions used for the definition of the diseases are functional.

n.b. If the claims are directed to a condition susceptible of being improved or prevented by selective interaction with a biological pathway, the claims can be regarded as clear only if instruction, in the form of experimental tests or any testable criteria, allowing the skilled person to recognise which conditions fall within the functional definition (and accordingly within the scope of the claims concerned) are available from the patent documents or from the general common knowledge. The selective interaction with a biological pathway itself cannot be considered as a therapeutic application.

CLAIMS:

1. A method for inducing promotion of neural cell differentiation of target cells comprising contacting said target cells for a suitable period of time with an effective amount of a compound of the general Formula I



wherein

Y is $-(CH_2)_m-$, -CH(OH)- or -C(=O)- , and m is 0 - 3 ;

X is H, alkyl, $-CH_2OH-$, CH_2Oacyl or $-CH_2$acyl; and

R is H, a cation, alkyl or optionally substituted aryl; provided that when Y is $-(CH_2)_m-$, m=0, and R is H or cation, X is not CH_2Oacyl.

2. A method for promoting neural activity in an individual comprising administering to the individual in need an effective amount of a compound of the general Formula I of Claim 1.

3. A method according to Claim 2, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.

4. A method for the prevention or treatment of disorders and diseases which can be prevented or treated by promoting neural cell differentiation and/or neural activity comprising administering to a person in need a therapeutically effective amount of a compound of Formula I of Claim 1.

5. A method according to Claim 4, wherein said disorders and diseases are mental disorders or diseases.

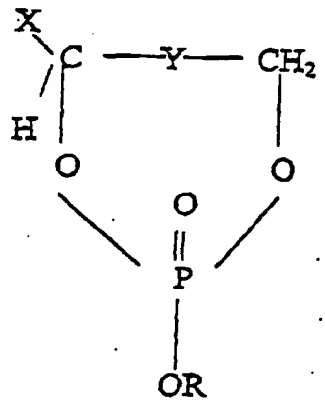
6. A method according to Claim 5, wherein said mental disorder or disease is schizophrenia or dementia.

7. A method according to Claim 4, wherein said disorders and diseases are neurodegenerative disorders or diseases.

8. A method according to any one of claims 1 to 7 wherein the compound of Formula I is selected from the group consisting of:

i. 1,3 cyclic glycerophosphate - **1,3 cGP;**
ii. 1,2 cyclic glycerophosphate - **1,2 cGP;**
iii. Phenyl 1,3 cGP – **P-1,3 cGP;**
iv. Phenyl 1,2 cGP – **P-1,2 cGP;**
v. 1,3 cyclic propanediol phosphate – **1,3 cPP;**
vi. 1,2 cyclic propanediol phosphate – **1,2 cPP;**
vii. Phenyl 1,3 cPP – **P-1,3 cPP;**
viii. Phenyl 1,2, cyclic propanediol phosphate – **P-1,2, cPP;**
ix. Cyclic dihydroxyacetone phosphate – **cDHAP;** and
x. Phenyl cyclic dihydroxyacetone phosphate - **P-cDHAP.**

9. Use of a compound of the general Formula I



wherein

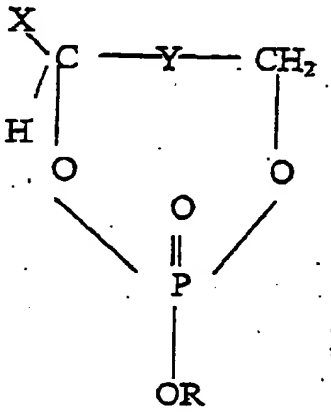
Y is $-(CH_2)_m-$, -CH(OH)- or -C(=O)- , and m is 0 - 3 ;

X is H, alkyl, -CH_2OH-, CH_2Oacyl or -CH_2acyl; and

R is H, a cation, alkyl or optionally substituted aryl; provided that when Y is -$(CH_2)_m$-, m=0, and R is H or cation, X is not CH_2Oacyl

for the preparation of a pharmaceutical composition for promoting neural cell differentiation.

10. Use of a compound of the general Formula I



wherein

Y is -$(CH_2)_m$-, -CH(OH)- or -C(=O)- , and m is 0 - 3 ;

X is H, alkyl, -CH_2OH-, CH_2Oacyl or -CH_2acyl; and

R is H, a cation, alkyl or optionally substituted aryl; provided that when Y is -$(CH_2)_m$-, m=0, and R is H or cation, X is not CH_2Oacyl for the preparation of a pharmaceutical composition for promoting neural activity.

11. Use according to Claim 10, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promoting of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.

12. Use according to Claim 9, for the prevention or treatment of disorders and diseases which can be prevented or treated by promoting neural cell differentiation and/or neural activity.

13. Use according to Claim 12, wherein said disorders and diseases are mental disorders or diseases.

14. Use according to Claim 13, wherein said mental disorder or disease is schizophrenia or dementia.

15. Use according to Claim 14, wherein said disorders and diseases are neurodegenerative disorders or diseases.

16. Use according to any one of Claims 9 to 15, wherein the compound of Formula I is selected from the group consisting of:

i. 1,3 cyclic glycerophosphate - **1,3 cGP;**

ii. 1,2 cyclic glycerophosphate - **1,2 cGP;**

iii. Phenyl 1,3 cGP – **P-1,3 cGP;**

iv. Phenyl 1,2 cGP – **P-1,2 cGP;**

v. 1,3 cyclic propanediol phosphate – **1,3 cPP;**

vi. 1,2 cyclic propanediol phosphate – **1,2 cPP;**

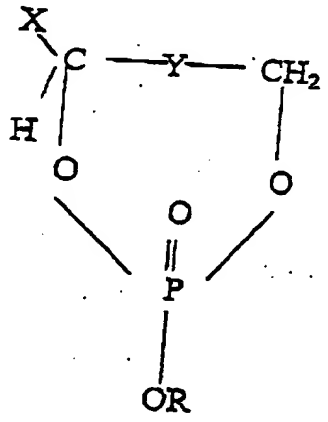
vii. Phenyl 1,3 cPP – **P-1,3 cPP;**

viii. Phenyl 1,2, cyclic propanediol phosphate – **P-1,2, cPP;**

ix. Cyclic dihydroxyacetone phosphate – **cDHAP;** and

x. Phenyl cyclic dihydroxyacetone phosphate - **P-cDHAP.**

17. A method for promoting neural activity in an individual comprising administering to the individual in need an effective amount of a compound of the general Formula I



wherein

Y is $-(CH_2)_m-$, -CH(OH)- or -C(=O)- , and m is 0 - 3 ;

X is H, alkyl, $-CH_2OH-$, CH_2Oacyl or $-CH_2$acyl; and

R is H, a cation, alkyl or optionally substituted aryl;

wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration condition other than dementia and nerve rescue.

18. A method for the prevention or treatment of disorders and diseases, other than dementia, which can be prevented or treated by promoting neural cell differentiation and/or neural activity, the method comprising administering to a person in need a therapeutically effective amount of a compound of Formula I of Claim 14.

19. A method according to Claim 18, wherein said disorders and diseases are mental disorders or diseases.

20. A method according to Claim 19, wherein said mental disorder or disease is schizophrenia.

21. A method according to Claim 19, wherein said mental disorder is a learning disability.

22. A method according to Claim 18, wherein said disorders and diseases are neurodegenerative disorders or diseases.

23. A method according to Claim 22, wherein said neurodegenerative disorder or disease is Alzheimer's disease or Parkinson's disease.

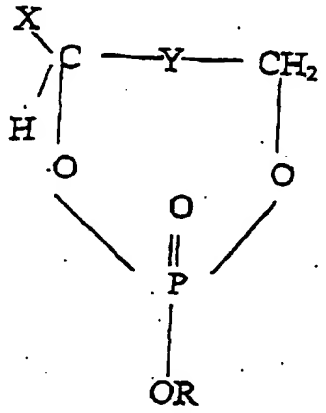
24. A method according to Claim 17, wherein said disorders or diseases result from exposure of an individual to harmful environmental factors or from a mechanical injury.

25. A method according to Claim 17, for the treatment of nerve rescue after nerve injury.

26. A method according to any one of claims 17 to 25 wherein said compound of general formula I is selected from the group consisting of

i. 1,3 cyclic glycerophosphate - **1,3 cGP;**
ii. 1,2 cyclic glycerophosphate - **1,2 cGP;**
iii. 3-acyl 1,2 cyclic glycerophosphate (cyclic lysophosphatidic acid) - **c-lysoPA;**
iv. Phenyl 1,3 cGP – **P-1,3 cGP;**
v. Phenyl 1,2 cGP – **P-1,2 cGP;**
vi. 1,3 cyclic propanediol phosphate – **1,3 cPP;**
vii. 1,2 cyclic propanediol phosphate – **1,2 cPP;**
viii. Phenyl 1,3 cPP – **P-1,3 cPP;**
ix. Phenyl 1,2, cyclic propanediol phosphate – **P-1,2, cPP;**
x. Cyclic dihydroxyacetone phosphate – **cDHAP;** and
xi. Phenyl cyclic dihydroxyacetone phosphate - **P-cDHAP.**

27. Use of a compound of the general Formula I



wherein

Y is $-(CH_2)_m-$, -CH(OH)- or -C(=O)- ,.and m is 0 - 3 ;

X is H, alkyl, $-CH_2OH-$, CH_2Oacyl or $-CH_2$acyl; and

R is H, a cation, alkyl or optionally substituted aryl; for the preparation of a pharmaceutical composition for promoting neural activity selected from the group consisting of promotion of neuronal outgrowth, promoting of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, nerve rescue and prevention of nerve degeneration conditions other than dementia.

28. Use according to Claim 27, for the prevention or treatment of disorders and diseases, other than dementia, which can be prevented or treated by promoting neural cell differentiation and/or neural activity.

29. Use according to Claim 28, wherein said disorders and diseases are mental disorders or diseases.

30. Use according to Claim 29, wherein said mental disorder or disease is schizophrenia.

31. Use according to Claim 29, wherein said mental disorder is a learning disability.

32. Use according to Claim 28, wherein said disorders and diseases are neurodegenerative disorders or diseases.

33. Use according to Claim 32, wherein said neurodegenerative disorders or diseases are Alzheimer's disease or parkinson's disease.

34. Use according to Claim 28, wherein said disorders or diseases result from exposure of an individual to harmful environmental factors or from a mechanical injury.

35. Use according to Claim 27, for nerve rescue after nerve injury.

36. Use according to any one of claims 27 to 35 wherein said compound of formula I is selected form the group consisting of

i. 1,3 cyclic glycerophosphate - **1,3 cGP;**

ii. 1,2 cyclic glycerophosphate - **1,2 cGP;**

iii. 3-acyl 1,2 cyclic glycerophosphate (cyclic lysophosphatidic acid) - **c-lysoPA;**

iv. Phenyl 1,3 cGP – **P-1,3 cGP;**

v. Phenyl 1,2 cGP – **P-1,2 cGP;**

vi. 1,3 cyclic propanediol phosphate – **1,3 cPP;**

vii. 1,2 cyclic propanediol phosphate – **1,2 cPP;**

viii. Phenyl 1,3 cPP – **P-1,3 cPP;**

ix. Phenyl 1,2, cyclic propanediol phosphate – **P-1,2, cPP;**

x. Cyclic dihydroxyacetone phosphate – **cDHAP;** and

xi. Phenyl cyclic dihydroxyacetone phosphate - **P-cDHAP.**